Preoperative Risk Score and Prediction of Long-Term Outcomes after Hepatectomy for Intrahepatic Cholangiocarcinoma

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BACKGROUND: Accurate prediction of prognosis for patients with intrahepatic cholangiocarcinoma (ICC) remains a challenge. We sought to define a preoperative risk tool to predict long-term survival after resection of ICC.

STUDY DESIGN: Patients who underwent hepatectomy for ICC at 1 of 16 major hepatobiliary centers between 1990 and 2015 were identified. Clinicopathologic data were analyzed and a prognostic model was developed based on the regression β-coefficients on data in training set. The model was subsequently assessed using a validation set.

RESULTS: Among 538 patients, most patients had a solitary tumor (median tumor number 1; interquartile range 1 to 2) and median tumor size was 5.7 cm (interquartile range 4.0 to 8.0 cm). Median and 5-year overall survival was 39.0 months and 39.0%, respectively. On multivariable analyses, preoperative factors associated with long-term survival included tumor size (hazard ratio [HR] 1.12; 95% CI 1.06 to 1.18), natural logarithm carbohydrate antigen 19-9 level (HR 1.33; 95% CI 1.22 to 1.45), albumin level (HR 0.76; 95% CI 0.55 to 0.99), and neutrophil to lymphocyte ratio (HR 1.05; 95% CI 1.02 to 1.09). A weighted composite prognostic score was constructed based on these factors: [9 + (1.12 × tumor size) + (2.81 × natural logarithm carbohydrate antigen 19-9) + (0.50 × neutrophil to lymphocyte ratio) + (−2.79 × albumin)]. The model demonstrated good performance in the testing (area under the curve 0.696) and validation (0.691) datasets. The model performed better than both the T categories (area under the curve 0.532) and the cumulative stage classifications in the American Joint Committee on Cancer staging manual, 8th edition (area under the curve 0.559). When assessing risk of death within 1 year of operation, a risk score ≥25 had a positive predictive value of 59.8% compared with a positive predictive value of 35.3% for American Joint Committee on Cancer staging manual, 8th edition T4 disease and 31.8% for stage IIIB disease.

CONCLUSIONS: Postsurgical long-term outcomes could be predicted using a composite weighted scoring system based on preoperative clinical parameters. The preoperative risk model can be used to inform patient to provider conversations and expectations before operation. (J Am Coll Surg 2018;226:393−403.

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Drs Sasaki and Margonis contributed equally to this work.

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Abbreviations and Acronyms

AJCC = American Joint Committee on Cancer
CA = carbohydrate antigen
HR = hazard ratio
ICC = intrahepatic cholangiocarcinoma
IQR = interquartile range
NLR = neutrophil to lymphocyte ratio
OS = overall survival

Although resection is the cornerstone of treatment for intrahepatic cholangiocarcinoma (ICC), outcomes after operation are frequently poor.[1-3] In fact, even among carefully selected patients, median survival after operation can be as low at 15 to 24 months and 5-year overall survival rates range from 20% to 40%.[4-6] The high incidence of recurrence after operation of ICC is difficult to explain. Specifically, more than one-half of patients who undergo curative intent resection of ICC experience recurrent disease within 2 years of operation.[7] Of note, nonoperative therapies, such as intra-arterial therapy and radiation therapy, have been reported to have similar long-term outcomes in some patients.[8] For example, select patients with inoperable ICC treated with intensity-modulated radiotherapy had a reported median overall survival (OS) of 30 months.[9] In a separate study, patients with advanced ICC treated with intra-arterial therapy had a median survival of 13 to 15 months, with better outcomes among patients who had a good radiologic response.[10] Given the high risk of recurrence, as well as some reported outcomes comparable with nonoperative therapy, better preoperative patient selection of ICC patients is necessary.[2]

Standardized preoperative risk assessment tools can help to identify patients at the time of treatment selection and thereby inform preoperative decisions around patient management. To this end, staging systems and prognostic models are currently used in many malignancies to facilitate treatment decisions and provide guidance on anticipated long-term outcomes.[11,12] Prognostic models that incorporate preoperative variables can be used to help evaluate and plan treatment selection. Unfortunately, the development and implementation of preoperative risk scores have been somewhat limited. Specifically, while several staging schemas and nomograms have been developed and validated for patients with resectable ICC, most models to date have used variables that can only be assessed postoperatively.[13-17] A prognostic model that allows for risk stratification at the time of treatment selection among patients with surgically resectable ICC has yet to be developed. As such, the objective of the current study was to develop a preoperative risk score for patients with surgically resectable ICC using an international, multi-institutional cohort of patients. Specifically, using preoperative information on liver function, morphology, and tumor biology, we sought to identify which patients derived the most benefit from resection of ICC.

METHODS

Study population

From 1990 to 2015, patients who underwent curative-intent liver resection for ICC at 16 major hepatobilliary centers in the US, Europe, Asia, and Oceania (Cleveland Clinic Foundation, Cleveland, Ohio; Johns Hopkins University, Baltimore, Maryland; Emory University, Atlanta, Georgia; Stanford University Medical Center, Stanford, California; University of Virginia Health System, Charlottesville, Virginia and Ottawa General Hospital, Ottawa, Canada, Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Yokohama City University, Yokohama, Japan; Royal Prince Alfred Hospital, Sydney, Australia, Fundeni Clinical Institute, Bucharest, Romania; Beaujon Hospital, Clichy, France; Curry Cabral Hospital, Lisbon, Portugal; San Raffaele Hospital, Milan, Italy; and Erasmus University Medical Centre Rotterdam, Rotterdam, The Netherlands) were identified. Patients who underwent macroscopically incomplete resection (R2) or patients with concurrent extrahepatic disease at the time of hepatectomy were excluded from the study. The study was approved by the IRBs of the respective institutions.

Preoperatively available data on liver function (ie albumin), tumor morphology (ie tumor size on imaging studies), tumor biology (ie preoperative carbohydrate antigen (CA) 19-9 level), and systemic inflammatory response (ie neutrophil to lymphocyte ratio [NLR]) were recorded. The primary end point of the study was OS, which was defined as the time from initial liver resection to the date of death or last follow-up.

Statistical analysis

Summary statistics were reported as frequencies with percentages or median values using interquartile ranges (IQR). Differences between categorical values were estimated using the chi-square test, and differences between continuous values were assessed with the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. The normality assumption was violated in the case of CA 19-9, as the distribution exhibited marked right skewness. Therefore, natural logarithm

transformation was used before assessing the impact of these variables on OS.

Before the analysis, the study cohort was randomly internally divided into a test and a validation sub-cohort. In the test sub-cohort, a number of possible preoperative predictors of survival (plus patient age) were selected on the basis of clinical experience and assessed through univariable analysis. Subsequently, a multivariable stepwise Cox regression analysis (backward elimination method) was performed to identify independent predictors of decreased OS. The proportionality of hazards assumption was confirmed using Schoenfeld's global test. Finally, the β-coefficients of the identified prognostic factors were used to construct a weighted composite prognostic score. The prognostic discrimination (the ability to differentiate between low and high risk patients) of the score was estimated with the aid of receiver operating characteristic curve analysis and calculation of the area under the curve, as described previously.[18] Subsequently, the prognostic discrimination of the score was internally validated in the validation sub-cohort. Analyses were performed using SPSS software, version 24 (IBM Corp) and STATA, version 13 (Stata Corp). A p value < 0.05 (2-tailed) was considered statistically significant.

RESULTS

Patient characteristics in the testing and validation sub-cohorts

A total of 538 adult patients met eligibility criteria and were included in the study population. Median follow-up was 25.6 months (IQR 12.4 to 47.7 months). A total of 283 patients died during the follow-up period and median, 1-, 3-, and 5-year OS was 39.5 months, 81.5%, 52.6%, and 39.0%, respectively. Table 1 summarizes the clinicopathologic characteristics of the study cohort. The study population was randomly divided into training and validation sub-cohorts, respectively. Specifically, the training sub-cohort consisted of 269 patients with a median follow-up of 26.4 months (IQR 13.8 to 47.3 months); a total of 141 patients died during the follow-up period and 1-, 3-, and 5-year OS was 82.1%, 55.0%, and 36.8%, respectively. The validation sub-cohort consisted of 269 patients, with a median follow-up of 25.3 months (IQR 11.4 to 47.8 months). A total of 142 patients died during the follow-up period and 1-, 3-, and 5-year OS was 80.9%, 50.3%, and 41.1%, respectively.

Table 2 summarizes the clinicopathologic characteristics of the training and validation sub-cohorts. The training and validation sub-cohorts were relatively

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	All patients (n = 538)
Age, y, median (IQR)	57 (49–64)
Sex, n (%)	
Male	348 (64.8)
Female	189 (35.2)
Region, n (%)	
Western	163 (30.3)
Eastern	375 (69.7)
Serum total bilirubin, mg/dL, median (IQR)	0.7 (0.5–1.0)
Serum albumin level, g/dL, median (IQR)	4.2 (3.9–4.5)
Aspartate transaminase, IU/L, median (IQR)	29.0 (22.0–42.0)
Alanine transaminase, IU/L, median (IQR)	28.0 (18.0–44.0)
Neutrophil to lymphocyte ration, median (IQR)	2.7 (2.0–4.1)
Serum carbohydrate antigen 19-9 level, IU/mL, median (IQR)	44.6 (17.0–221.0)
Nodules, n (%)	
Solitary	480 (89.2)
Multiple	58 (10.8)
Maximum diameter of the tumor, cm, median (IQR)	5.7 (4.0–8.0)
Pathology-proven satellite lesions, n (%)	
Negative	437 (81.2)
Positive	101 (18.8)
Tumor morphology type (n = 521), n (%)	
Mass-forming type	494 (94.8)
Non-mass-forming type	27 (5.2)
Histologic differentiation (n = 530), n (%)	
Well/moderate	463 (87.4)
Poor	67 (12.6)
Vascular invasion, n (%)	
Negative	381 (70.8)
Positive	157 (29.2)
Resection margin, n (%)	
R0	493 (91.6)
R1	45 (8.4)
American Joint Committee on Cancer 8th ed T stage, n (%)	
I	296 (55.0)
II	153 (28.4)
III	68 (12.6)
IV	21 (3.9)
Lymph node status, n (%)	
Nx	185 (34.4)
N0	262 (48.7)
N1	91 (16.9)

IQR, interquartile range; Nx, no pathologic lymph node status assessment.

Table 2. Comparison of Patient Characteristics among Training vs Validation Datasets

Characteristic	Training set (n = 269)	Validation set (n = 269)	p Value
Age, y, median (IQR)	58 (51–66)	57 (49–64)	0.739
Sex, n (%)			0.321
Male	180 (66.9)	168 (62.5)	
Female	89 (33.1)	101 (37.5)	
Region, n (%)			0.851
Western	80 (29.7)	83 (30.9)	
Eastern	189 (70.3)	186 (69.1)	
Serum total bilirubin, mg/dL, median (IQR)	0.7 (0.5–1.0)	0.7 (0.5–1.0)	0.908
Serum albumin level, g/dL, median (IQR)	4.2 (3.9–4.5)	4.2 (4.0–4.5)	0.924
Aspartate transaminase, IU/L, median (IQR)	30.3 (22.1–44.0)	28.0 (21.0–38.4)	0.026
Alanine transaminase, IU/L, median (IQR)	30.0 (18–44.9)	27.0 (18.0–41.0)	0.181
Neutrophil to lymphocyte ratio, median (IQR)	2.7 (2.1–4.1)	2.9 (2.0–4.1)	0.703
Serum carbohydrate antigen 19-9 levels, IU/mL, median (IQR)	42.6 (17.0–240.0)	48.6 (18.2–218.5)	0.379
No. of nodules, n (%)			0.677
Solitary	242 (90.0)	238 (88.5)	
Multiple	27 (10.0)	31 (11.5)	
Maximum diameter of the tumor, cm, median (IQR)	5.8 (4.0-8.0)	5.5 (3.6-8.0)	0.459
Pathology-proven satellite lesions, n (%)			0.008
Negative	206 (76.6)	231 (85.9)	
Positive	63 (23.4)	38 (14.1)	
Tumor morphology type (n = 521), n (%)			1.000
Mass-forming type	247 (94.6)	247 (95.0)	
Non-mass-forming type	14 (5.4)	13 (5.0)	
Histologic differentiation (n = 530), n (%)			0.601
Well/moderate	229 (86.4)	234 (88.3)	
Poor	36 (13.6)	31 (11.7)	
Vascular invasion, n (%)			1.000
Negative	191 (71.0)	190 (70.6)	
Positive	78 (29.0)	79 (29.4)	
Resection margin, n (%)			0.534
R0	244 (90.7)	249 (92.6)	
R1	25 (9.3)	20 (7.4)	
American Joint Committee on Cancer 8th T stage, n (%)			
I	153 (53.2)	143 (53.2)	0.898
II	74 (29.4)	79 (29.4)	
III	29 (14.5)	39 (14.5)	
IV	13 (4.8)	8 (3)	
Lymph node status, n (%)			0.021
Nx	104 (38.7)	81 (30.1)	
N0	130 (48.3)	132 (49.1)	
N1	35 (13.0)	56 (20.8)	

IQR, interquartile range; Nx, no pathologic lymph node status assessment.

well balanced; in fact, only a small subset of variables differed, including median aspartate transaminase levels (30.3 IU/L: testing cohort vs 28.0 IU/L: validation cohort; p = 0.026), frequency of pathology-proven satellite lesions (23.4%: testing cohort vs 14.1%: validation cohort; p = 0.008), and incidence of metastatic lymph nodes (13.0%: testing cohort vs 20.8%: validation cohort; p = 0.021).

Table 3. Factors Associated with Survival after Hepatectomy for Intrahepatic Cholangiocarcinoma

Factor	p Value	Coefficient	SE	Wald χ^2	Hazard ratio	95% CI
Training set						
Serum albumin	0.047	−0.279	0.150	3.8	0.76	0.55−0.99
NLR	0.009	0.050	0.018	7.2	1.05	1.02−1.09
LogN CA19-9	<0.001	0.281	0.041	43.7	1.33	1.22−1.45
Size (per cm)	<0.001	0.112	0.026	18.6	1.12	1.06−1.18
Validation set						
Serum albumin	0.026	−0.328	0.148	4.9	0.72	0.54−0.96
NLR	0.008	0.046	0.017	7	1.05	1.01−1.08
LogN CA19-9	<0.001	0.263	0.040	42.3	1.30	1.20−1.41
Size (per cm)	<0.001	0.103	0.025	15.8	1.11	1.06−1.17

CA 19-9, carbohydrate antigen 19-9; LogN, natural logarithm; NLR, neutrophil to lymphocyte ratio; Nx, no pathologic lymph node assessment.

Analysis of preoperatively available, independent predictors of overall survival in the testing sub-cohort

On stepwise Cox regression multivariable analyses of the training dataset, preoperative factors associated with long-term survival included albumin level (hazard ratio [HR] 0.78; 95% CI 0.59 to 0.98), tumor size (HR 1.12; 95% CI 1.06 to 1.18), natural logarithm CA 19-9 level (HR 1.33; 95% CI 1.22 to 1.45), and neutrophil to lymphocyte ratio (NLR) (HR 1.05; 95% CI 1.02 to 1.09) (Table 3). A risk score equation was constructed based on the β-coefficients of these 4 independent prognostic factors. The derivative scores in the training set and validation set ranged from −9.0 to 53.0; for ease, a fixed constant valued of 9 was added to weight the score to avoid a negative score. In turn, the final weighted composite prognostic model was: [9 + (−2.79 × albumin) + (0.50 × NLR) + (2.81 × natural logarithm CA 19-9) + (1.12 × tumor size)]. Figure 1 demonstrates the distribution of the scores in the training, validation, and whole cohort. Based on Harrel's C-index, the discriminatory performance in the training set was 0.696 (95% CI 0.630 to 0.755); a comparable performance was observed in the validation set (0.691; 95% CI 0.626 to 0.748).

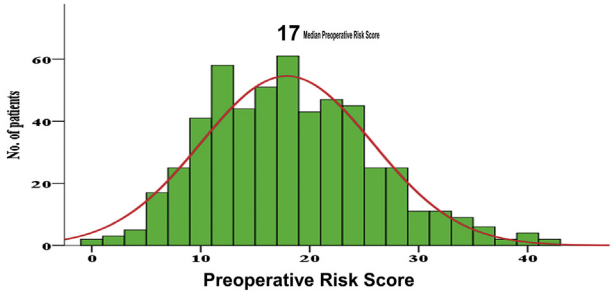

Figure 1. The distribution of the preoperative risk scores was normally distributed over the entire cohort with a median preoperative risk score of 17.

Patients were then assigned to different score categories according to mortality risk: category 1 (score: 0 to 9), category 2 (score: 10 to 19), category 3 (score: 20 to 29), category 4 (score: 30 to 39), and category 5 (score: >40). Using the prognostic score, patients with ICC could be incrementally stratified with regard to median OS and 5-year OS (Fig. 2). Specifically, category 1 patients had a median OS of not reached and a 5-year OS of 66.1%; category 2 patients had a median OS of 23.5 months and a 5-year OS of 19.2%; category 3 patients had a median OS of 10.9 months and a 5-year OS of 14.7%; and category 4 patients had a median OS of 5.1 months and a 5-year OS of 0% ($p < 0.001$). Notably, the preoperative risk score was also associated with adverse postoperative pathologic features (Table 4). Specifically, a higher preoperative risk score was correlated with the presence of an increased risk of adverse histopathologic features, such as satellite lesions, vascular invasion, and poor tumor differentiation (all $p < 0.05$).

Discriminatory ability of the proposed preoperative score vs the American Joint Committee on Cancer, 8th edition, staging system

The performance of the scoring system was assessed relative to the 8th edition of the American Joint Committee on Cancer (AJCC) T category designations, as well as overall AJCC 8th edition stage (Fig. 3). Of note, the prognostic discrimination ability of the preoperative prognostic score (c-index 0.693; 95% CI 0.650 to 0.742) was better than the performance of the AJCC 8th edition T category designations (c-index 0.532; 95% CI 0.483 to 0.580) ($p < 0.001$) (Fig. 4). The preoperative score also outperformed the overall AJCC staging system. Specifically, Harrell's C-index

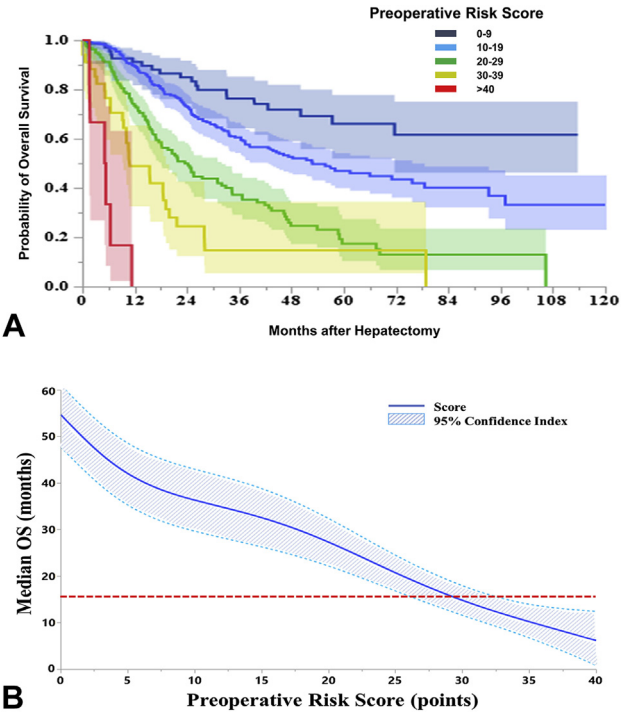

Figure 2. (A) Using the preoperative prognostic score, patients were categorized into different mortality risk group relative to long-term overall survival. (B) Of note, a high preoperative risk score was associated with a strong positive predictive value to predict the chance of death within 15 months of operation. OS, overall survival.

for the preoperative score was 0.693 (95% CI 0.650 to 0.742) vs 0.559 (95% CI 0.498 to 0.619) for the full AJCC staging system (both $p < 0.001$). Of note, in assessing risk of death within 15 months after surgery among patients in the entire cohort, a risk score ≥ 25 had a positive predictive value of 59.8% compared with a positive predictive value of 35.3% for T4 disease and 31.8% for stage IIIB disease according to the AJCC, 8th edition. Interestingly, patients with a preoperative score >30 had an extremely adverse prognosis with a positive predictive value of death within 15 months after surgery of 64.9% (Fig. 2B).

DISCUSSION

To date, many prognostic schemes—including the most commonly used AJCC staging system—largely have focused on factors obtained postoperatively on pathologic assessment of the specimen. Although risk stratification and prediction of prognosis after resection are important, more data are needed to assess long-term risk of death before operation. Preoperative assessment of long-term survival benefit is particularly important for surgical procedures potentially associated with major morbidity, as well as those diseases that generally have a poor prognosis. To this point, resection of ICC often necessitates a major hepatic resection and can be associated with a higher risk of postoperative morbidity than liver procedures for other indications (eg liver metastasis).[19] In addition, ICC is an aggressive tumor that can often be associated with a poor prognosis, even among patients undergoing resection with curative intent.[20] As such, better preoperative prognostic stratification of patients with ICC can help direct clinical decision making, as well as provide information to help counsel patients. The current study was important because by using a large international multi-institutional cohort of patients with ICC, 4 preoperative factors were identified that were strongly associated with postoperative OS. Specifically, albumin level, tumor size, CA 19-9 level, and NLR were each correlated with long-term prognosis. Using these factors, a novel preoperative score was developed and validated that was able to stratify long-term survival after operation. Of note, the preoperative score had good discriminatory ability on both the testing and validation cohorts.

In addition, the preoperative score had a number of significant advantages over previous prognostic models. First, it is, to our knowledge, among the only prognostic scores to date that can be used preoperatively among patients with surgically resectable ICC.[11,12] In turn, the preoperative model allows for risk stratification at the time of treatment selection, facilitating treatment decisions (eg preoperative chemotherapy, nonoperative ICC treatment modalities).[21] In addition, the score might enable surgeons to offer patients a more accurate prognostic "forecast" at the time of the initial preoperative consultation.[22]

Of note, the preoperative score outperformed the 8th edition of the AJCC staging system, even though the AJCC staging scheme mostly relies on postoperative pathologic data.[23] The better performance of the preoperative model was likely attributable to several factors. In particular, the current model had the advantage of using a continuous risk score for patients with ICC. The fact that we used a continuous, rather than categorical, model could help explain the prognostic power of the model, as data from other malignancies have noted that that the accuracy of continuous risk scores is consistently superior vs comparable models that use designated cutoff values.[24] In particular, the use of binary variables to classify variables into categorical groupings can lead to loss of prognostic power.[24] In addition to how the data were analyzed, the score incorporated a variety of prognostic determinants that accounted for a wide range of factors, including functional liver status, tumor morphology, tumor biology, and host-tumor interactions—all of which

Table 4. Cumulative Preoperative Risk Score According to Different Clinicopathologic Characteristics

Characteristic	Preoperative risk score	
	Median (IQR)	p Value
Pathology-proven satellite lesions		0.001
Negative	16.7 (11.6–222.4)	
Positive	18.9 (14.5–24.8)	
Tumor morphology type		0.165
Mass-forming type	17.1 (12.1–22.5)	
Non-mass-forming type	19.4 (12.4–24.2)	
Histologic differentiation		0.006
Well/moderate	16.8 (11.9–22.4)	
Poor	20.3 (15.8–23.4)	
Vascular invasion		<0.001
Negative	16.7 (12.0–21.5)	
Positive	19.4 (13.4–24.6)	
Resection margin		0.118
R0	17.2 (2.0–22.5)	
R1	19.3 (14.8–24.8)	
American Joint Committee on Cancer 8th ed T stage		<0.001*
I	15.4 (11.1–21.1)	
II	17.9 (12.4–23.5)	
III	19.4 (16.6–24.6)	
IV	23.7 (20.0–28.6)	
Lymph node status		<0.001*
Nx	14.4 (10.0–18.4)	
N0	18.5 (13.2–23.6)	
N1	20.7 (15.9–25.3)	

*Kruskal-Wallis test.
IQR, interquartile range; Nx, no pathologic lymph node status assessment.

can play important roles in the pathophysiology and prognosis of ICC.[4]

The preoperative score incorporated information on host-tumor interaction through the inclusion of NLR, which is a readily available marker of systemic inflammation.[25] Importantly, chronic inflammation induced by hepatitis, steatosis, liver flukes, hepatolithiasis, or primary sclerosing cholangitis can be associated with an increased risk of ICC development.[26] In turn, the extent of the inflammatory response can impact long-term outcomes.[27,28] More specifically, an elevated NLR can be indicative of neutrophilia, lymphopenia, or a combination of both. Neutrophilia can induce a favorable tumor microenvironment by secreting molecules, such as vascular endothelial growth factor, matrix metallopeptidase 9, and reactive oxygen species, that degrade the extracellular matrix, promoting angiogenesis, tumor growth, and metastasis.[29,30] On the other hand, the presence of lymphopenia might signify lower counts of tumor-specific $CD8^+$ cytotoxic T cells and, consequently, reduce the capacity to combat tumor cells through immune surveillance.[31-33] Although NLR is a relatively simple proxy of host-tumor interactions, its availability, ease of use, and robust association with outcomes suggested that it could be a useful risk score component.

Given the important role of chronic inflammation in the pathophysiology of ICC, factors that counter-balance the harmful effects of inflammation and oxidative stress can result in improved outcomes. Specifically, albumin is known to play a major role in the neutralization of reactive oxygen and nitrogen species that, in turn, can cause DNA damage and promote carcinogenesis.[34-36] Importantly, low albumin or albumin-based markers have been associated with worse survival for several other malignancies. In particular, in the case of primary liver tumors, albumin has been demonstrated to suppress directly the proliferation of HCC cell line, thereby suggesting that albumin might have an antiproliferative effect.[37] In addition, as a proxy of liver function, albumin levels have been associated with outcomes, with increased albumin levels indicating conserved liver function and a reduced risk of death.[38]

In addition to accounting for host-tumor interplay and liver functional status, the preoperative score also incorporated an established marker of tumor biology—CA 19-9. Preoperative CA 19-9 was been reported to be an independent predictor of OS in several studies from Asia and North America. Specifically, Ohtsuka and colleagues[39] reported on the prognostic impact of CA 19-9 for patients with resected ICC; in a separate study, Wang and colleagues[40] similarly noted the prognostic impact of CA 19-9 and incorporated this preoperative laboratory value into a prognostic nomogram, which largely otherwise consisted of postoperative factors. Interestingly, the authors noted that the discriminatory ability of the nomogram was mainly attributable to the prognostic power of CA 19-9, as the nomogram was otherwise similar to previous staging systems and prognostic models.[40] The CA 19-9 cutoff levels have been difficult to determine, however, and various cutoff values ranging from 37 to 100 IU/mL have been used.[41] The current study avoided this problem by incorporating CA 19-9 values into the preoperative prognostic score as a continuous variable, thereby avoiding the sacrifice of prognostic information associated with reliance on categorical classifications of such data.

Tumor size was also incorporated into the preoperative prognostic score. Interestingly, the importance of tumor size in ICC has been controversial. Although tumor size was not incorporated into the 7th edition of the AJCC staging system,[42] a subsequent, adequately powered meta-analysis reported that large tumor size was indeed associated with worse long-term outcomes.[33] Specifically,

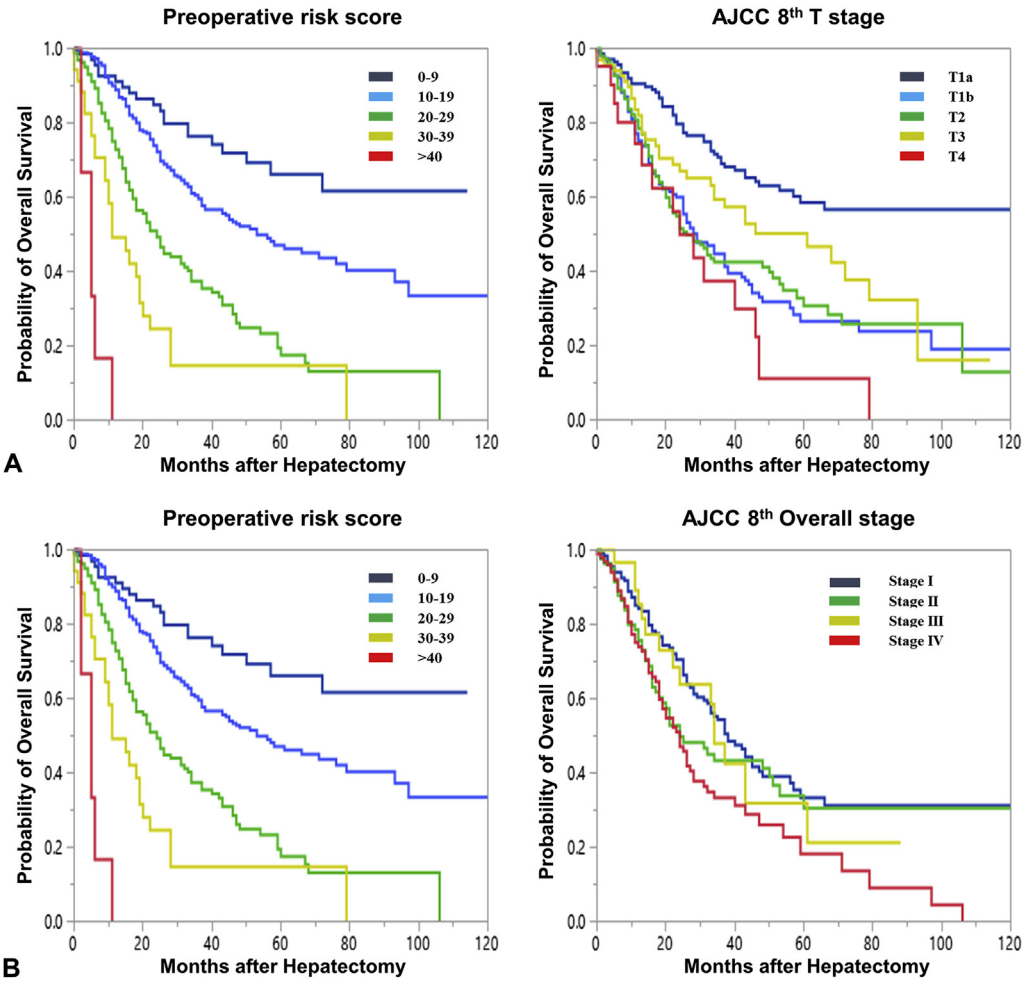

Figure 3. The performance of the scoring system was assessed relative to the (A) 8th edition of the American Joint Committee on Cancer (AJCC) T category designations and (B) overall final AJCC stage. Although the preoperative risk model stratified overall survival in an incremental fashion, there was poor separation of survival curves according to the T categories as patients with T2, T3, and T4 disease had overlapping survival. In addition, the preoperative risk model similarly had an improved ability to stratify survival compared with overall AJCC staging, which performed poorly.

Mavros and colleagues[43] reported that the risk of worse OS increased incrementally with each 1-cm increase in tumor diameter. In the current study, when analyzed as a continuous variable, we similarly noted that tumor size had a prognostic impact on outcomes. Although several previous studies failed to demonstrate an association of tumor size with prognosis, the relatively small number of patients with tumors smaller than the AJCC suggested a 5-cm cutoff value might have limited the statistical analyses.[10] In the current study, 198 patients had an ICC tumor <5 cm in diameter, suggesting the data were less skewed in terms of tumor size than previous studies. The use of both preoperative and postoperative variables in the predictive models might have also negated the prognostic power of tumor size in previous studies. For example, tumor size can exhibit strong collinearity with histologic tumor grade, which is another important postoperative determinant of prognosis.[44] As the current study did not include postoperative variables, the relative prognostic power of tumor size might have been enhanced by its capacity to serve as a proxy for the presence of the aforementioned histopathologic features. To this end, a higher preoperative risk score was correlated with the presence of an increased risk of adverse histopathologic features, such as vascular invasion and poor tumor differentiation.

There has not been a randomized trial comparing the efficacy of surgery vs nonoperative treatments, such as

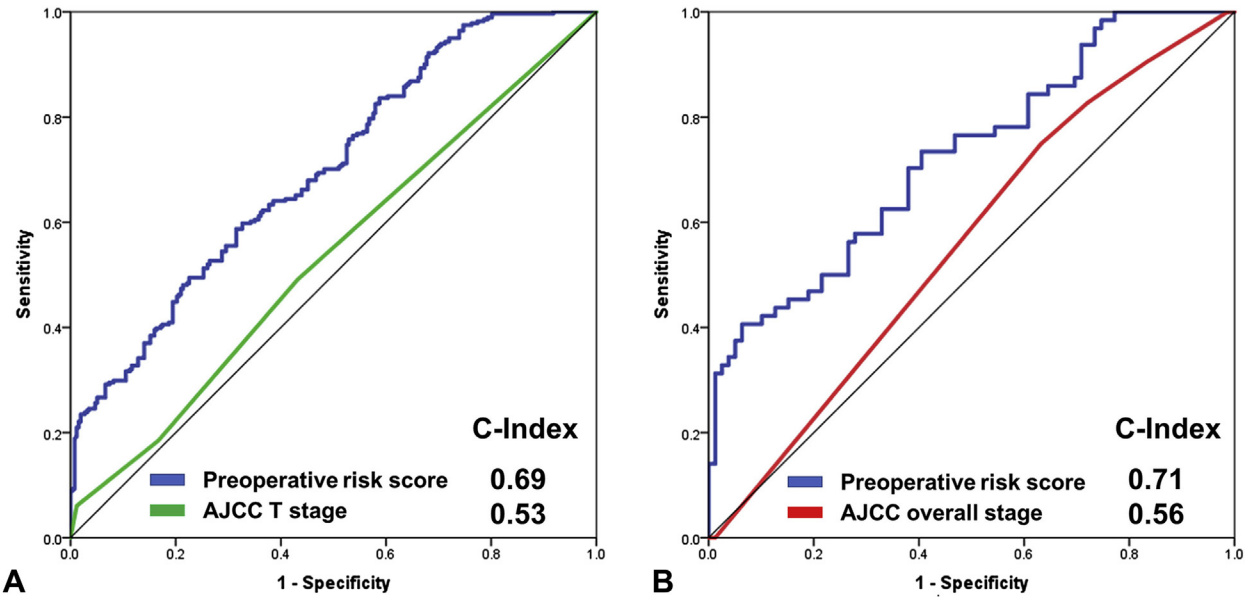

Figure 4. In assessing overall prognostic discrimination in the validation subset, (A) the intrahepatic cholangiocarcinoma risk score performed significantly better than the American Joint Committee on Cancer (AJCC) T categories. (B) The preoperative score risk also outperformed final AJCC overall staging based on final pathology.

intra-arterial or radiation therapy. Although these groups of patients are often heterogeneous and difficult to compare, the data suggest that a subgroup of patients with aggressive disease derive minimal benefit from surgery and may be managed with nonoperative approaches.[8-10] In fact, some patients with inoperable ICC treated with either intra-arterial therapy or intensity-modulated radiotherapy have had reported outcomes that were not too dissimilar to the results of some patients treated with surgery.[9,10] In turn, these data suggest that a subset of patients with technically operable disease might not derive an incremental benefit from resection compared with other nonoperative modalities. To this point, the proposed score was designed using disease-related factors that could be identified in the preoperative setting, rather than treatment- or postoperative-related variables. In this way, the score can help identify patients who might benefit from consideration of other therapeutic approaches, including preoperative chemotherapy. Indeed, our group previously reported that a subset of patients with ICC can benefit from the use of preoperative chemotherapy.[2]

The current study had several limitations. Although data from multiple institutions increased the sample size, some degree of heterogeneity in terms of diagnostic, treatment, and follow-up protocols among the participating institutions was likely. Nonetheless, the use of an international, multi-institutional study design provided greater statistical power and increased the generalizability of the results. Although the preoperative score was assessed using an internal test dataset, external validation will be required, particularly in cohorts that might have been under-represented in the current study.

CONCLUSIONS

The current study defined and validated a preoperatively assessable, continuous risk score for patients with surgically resectable ICC. Importantly, the proposed score not only accounted for a variety of factors, such as tumor morphology, tumor biology, liver function, and host-tumor interactions, but also outperformed the AJCC 8th edition staging system for ICC. In turn, the preoperative risk model can be used to inform preoperative consultations and guide the design of future studies aimed to determine the most appropriate treatment for patients with different risk profiles.

Author Contributions

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Critical revision: Sasaki, Margonis, Andreatos, Bagante, Weiss, Barbon, Popescu, Marques, Aldrighetti, Maithel, Pulitano, Bauer, Shen, Poultsides, Soubrane, Martel, Koerkamp, Guglielmi, Itaru, Aucejo, Pawlik

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Discussion

DR CHARLES SCOGGINS (Louisville, KY): This paper is an example of the quality work that can be done when good surgeons gather their data together and collaborate for the common good. This model uses factors available in the preoperative setting. Although I can appreciate that it is moderately predictive and seems to provide valuable prognostic information, you did demonstrate that it is associated with pathologic markers that are more commonly used for predicting survival. Why not expand your model and include factors such as nodal status and margin status? It might enhance the model and make it even more predictive.

Many have sought to implicate systemic inflammation in a variety of diseases, including just about every cancer you can think of. You used a common surrogate for inflammation—the neutrophil-to-lymphocyte ratio. In your multivariate model, the hazard ratio for this factor was only 1.05, indicating a 5% higher risk. Do you think this is the best marker for inflammation? What happens to your predictive model if you leave it out?

Finally, how would you use this scoring system clinically? If you have a preoperative patient with a poor score, would you offer him or her another form of therapy? Systemic chemotherapy combined with drug-eluting bead chemoembolization might have a similar survival for such patients. Would you deny a resectable patient a resection based on your score?

DR MARIA B MAJELLA DOYLE (St Louis, MO): As we have heard, the authors are presenting work from an outstanding multi-institutional collaboration between 16 international centers, on outcomes after resection for intrahepatic cholangiocarcinoma (ICC) in more than 500 patients. Based on their results, the authors have created and validated a preoperative scoring system as a tool to predict prognosis after resection using preoperatively available clinical parameters.

First, what was the role was of neoadjuvant therapy for the study patients? Does neoadjuvant therapy affect the usefulness of the score? Additionally, if patients receive neoadjuvant therapy, can they improve their score or prognosis after they have had neoadjuvant therapy?

Second, can you comment on recurrence-free survival, which is not provided in the current manuscript? It seems to me that this would be a critically important factor in prognosticating cancer-specific survival.

Finally, the role of liver transplantation for early hepatocellular carcinoma and for selective hilar cholangiocarcinoma patients is well established. What do you think is the role of liver transplantation in ICC? There have been some studies looking at transplantation for early ICC with excellent results. Were any of the patients in the study considered for liver transplantation for their early ICC?

DR LEONIDAS KONIARIS (Indianapolis, IN): Did all of the institutions do lymphadenectomy for the ICCs? If they did, why do you think lymph nodes did not seem to make a difference? If lymph nodes do not make a difference, do you need to perform a lymphadenectomy for ICC?

DR CLIFFORD KO (Los Angeles, CA): I wanted to get your opinion on the types of data we would use for a prognostic model. When we made the NSQIP Risk Calculator, we had all kinds of variables that we thought were important for patient comorbidities. In a cancer situation with the American Joint Committee on Cancer, we are going on cancer information with intermediate